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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/416,384	10/12/1999	MARTA BLUMENFELD	GENSET.045AU	6101

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	27

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/416,384	Blumenfeld et al
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 28, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *58, 62, and 73-75* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *58, 62, and 73-75* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *14, 24*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 58, 62, and 73-75 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of polypeptides termed G713 proteins in the specification, antibodies against the G713 proteins, and a method of use of the antibody for detection of the G713 protein.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The only cited utilities identified by the examiner are to detect the protein itself, to make antibodies and to screen drugs. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the protein. No well established utilities for this specific G713 protein are identified in either the specification or in the cited prior art.

Substantial utility

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. Here, the evidence (in the form of published prior art) provided by applicant is argued to support the position that the presence of Glutamine repeats is a substantial utility which is specific to this G713 protein. The prior art, such as Perutz et al (Current Opinion Structural Biol. (1996) 6:848-858), teaches that several diseases are associated with glutamine repeats. This glutamine repeat utility would therefore be based upon the fact that in several other proteins, such as the Huntington's disease gene, or Bulbar muscular dystrophy, glutamine repeats were found to be responsible for the disease state. Applicant thus contends that the presence of these Glutamine repeats in a novel protein would be suggestive of a disease state, perhaps a neurological type disorder.

As noted in the utility guidelines, methods of treating unspecified diseases, basic research on a product to identify properties, intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials). If there were evidence of the association of all glutamine repeat containing proteins or the G713 protein itself with any disease state, this evidence might be sufficient to provide a substantial utility. First, there is NO data in the specification showing expansion of the CAG repeats in this particular protein, and it is the expansion of repeats which is the disease causing element. Many genes comprise glutamine, and many have glutamine repeats. A search of STN revealed that 14,560 sequences in the database which had a 3 repeat sequence of CAGCAGCAG, of which 6,723 sequences were

associated with human sequences. Second, not all glutamine repeats are associated with a disease state. For example, Kashima et al (J. Biochem. (1987) 102:725-32) notes "These results suggest that the consecutive glutamine repeats do not play a role in the biological and immunological activities of MIL-2, but that the peptide sequence around them does, and the species hierarchy that MIL-2 does not act on human lymphocyte is not due to the presence of glutamine repeats in MIL-2 (abstract)." Kashima expressly demonstrates that in the MIL-2 protein, glutamine repeats do not play a role, and would not be linked to any biological or functional role of the protein. Thus, glutamine repeats represent one of a number of elements which may or may not cause a protein to be associated with a disease and this element does not support a substantial utility for an unknown protein with unknown function which is not associated with any disease.

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, then the substantial utility of the G713 protein is, at best, a relationship to an association with glutamine repeats. This utility is not specific because Perutz, as noted above, has identified many different proteins with glutamine repeats, all of which are associated with different diseases and Kashima has identified at least one protein not disease associated with glutamine repeats. Thus, the presence of glutamine repeats does not provide a specific utility because there is no direct or even indirect connection made between any particular utility and the G713 protein. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of

what condition can be diagnosed". Here, there is no disclosure of any condition which can be diagnosed and hence, no specific utility.

Finally, with regard to the utility analysis, the current situation directly tracks Example 4 of the utility guidelines, where a protein of entirely unknown function was characterized as lacking utility.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 58, 62, and 73-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Nature of Invention

Claims 58, 62 and 73-75 are drawn to a G713 protein and methods of detection of this protein or gene product. The nature of this invention is a macromolecular polymer, in particular, a protein, with no other associated information. This is an invention in a subject area which is well recognized as unpredictable.

Breadth of the claims

The claims are drawn to the particular protein.

Amount of Guidance in the Specification

The specification discloses the entire sequence of the protein, but identifies no particular use for the protein and the asserted utility is the presence of CAG repeat elements. As noted in the utility rejection above, this utility is not found to be substantial nor specific and consequently, the specification provides NO guidance regarding how to use this protein.

Working Examples

There are NO working examples in which this G713 protein is used in any assay for detection or diagnosis of any disease or any other related utility.

Amount of Guidance in Prior Art

As noted in the utility rejection above, the prior art provides no guidance with regard to the particular function of the G713 protein and does not even provide support or guidance for glutamine repeat containing proteins having a particular use or association. As Kashima et al (J. Biochem. (1987) 102:725-32) notes "These results suggest that the consecutive glutamine repeats do not play a role in the biological and immunological activities of MIL-2, but that the peptide sequence around them does, and the species hierarchy that MIL-2 does not act on human lymphocyte is not due to the presence of glutamine repeats in MIL-2 (abstract)." Kashima expressly demonstrates that in the MIL-2 protein, glutamine repeats do not play a role, and would not be linked to any biological or functional role of the protein.

Skill in the Art

While no evidence is adduced, the examiner believes the skill in the art would be considered high.

Predictability of the Art

The art in biotechnology, as relates to the association of diseases with particular genes, is highly unpredictable. For example, Applicant argues that a particular chromosomal location is associated with schizophrenia. In Wright et al (Schizophrenia Research (2001) 47:1-12), Wright notes that over 16 studies have been performed which purport to associate HLA chromosomal locations with schizophrenia (Table 2). However, Wright notes that "Two recently reported investigations that controlled for most of the confounders discussed above found no evidence of association of HLA with schizophrenia (page 9, column 1). Thus, if Wright's review article and the two 1999 studies are correct, over 16 different studies published from 1975 to 1996 incorrectly linked schizophrenia and HLA. This strongly supports the unpredictability in this linkage of schizophrenia with chromosomal locations given the conflicting results of over 60 different studies (page 5, column 1).

Quantity of Experimentation

An immense amount of experimentation would be required in order to define whether this protein is associated with any particular disease state. In order to acquire statistically significant evidence of an association with a neurological or other disease, dozens of patients in each of the many hundreds of different possible disease states would need to be subjected to collection of samples for analysis of their DNA, followed by analysis and the inventive efforts of determining if any association exists. This is a very large quantity of experimentation.

Determination

In view of the unpredictable nature of the invention, the absence of any guidance in the specification for a substantial and specific use, the absence of any working examples in the specification, the negative teachings in the prior art, the extreme unpredictability of the invention, and the large amount of experimentation necessary balanced against the high level of skill in the art and the relatively narrow breadth of the claims, it is concluded that undue experimentation would be required to use this invention as claimed.

Response to Arguments

5. Applicant's arguments filed February 28, 2002, have been fully considered but they are not persuasive.

Applicant argues that the current application has substantial and specific utility. Applicant argues that the issue for substantial utility is whether it is more likely than not that proteins containing polyglutamine repeats are associated with neurodegenerative diseases. Applicant argues that it is more likely than not based upon the expression of the G713 protein in the brain, the association of 12 diseases with CAG repeat containing proteins.

However, these arguments fail to address the central question implicated in the analysis of substantial utility. As the Utility guidelines note, "Utilities that require or constitute carrying out further research to identify or reasonably confirm a "Real world" context of use are not substantial utilities (page 6 of guidelines)". The current case represents a situation where the protein lacks any known substantial utility. Contrary to applicant's arguments, the protein is NOT shown to be associated with any neurodegenerative disease, the protein is ONLY a candidate

gene for such an association. The association of the genomic region is not significant because it does not associate this protein with schizophrenia, since many genes may be within the region. The argument that the protein is expressed in brain is not persuasive given that Applicant states that thousands of proteins are expressed in brain, many of which have no particular phenotype associated with them.

Applicant argues that the use of three glutamine repeats in screening the genomic database is not a fair comparison because G713 has more than 3 repeat sequences. Applicant is relying, in argument, upon the association of glutamine repeat sequences with neurological disease. Therefore, it is perfectly fair to ask whether glutamine repeat sequences alone are limited to such an association. As the finding of 6,723 human sequences with 3 CAG repeating units shows, no such association can be made for all glutamine repeats. As a follow up, however, for 4 CAG repeating units, a search in STN finds 3,882 such human sequences. For 5 CAG repeating units, a search in STN finds 1,773 such human sequences. For 6 CAG repeating units, a search in STN finds 1,068 such human sequences. For 7 CAG repeating units, a search in STN finds 646 such human sequences. Even for 9 CAG repeating units, a search in STN still finds 310 such human sequences. Thus, even 9 CAG repeating units are found in a large number of human sequences, including 249 different publications, no assoication is found solely with neurological disease and glutamine repeating sequences.

This situation tracks example 5 of the Utility guidelines, where a protein is characterized, and in that example, some function was found for the protein unlike here. However, that function

was found insufficient because further experimentation was necessary to attribute a use to the protein. The Supreme Court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The Court in Brenner v. Manson, 383 U.S. 519 (1966) held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a protein of as yet undetermined function or biological significance.

With regard to substantial utility, there must be some correlation or relationship between the claimed protein and a disease or disorder. The presence of a protein in tissue that is derived from disease cells is not sufficient for establishing a substantial utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed protein to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed protein is either present only in disease tissue to the exclusion of normal tissue or

is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed protein as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed protein or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed protein or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

With regard to specific utility, Applicant traverses the cited Perutz and Kashima papers. Applicant argues that Perutz teaches some neurodegenerative diseases associated with glutamine repeats. This does not detract from the central point supported by Perutz, which is that glutamine repeats alone are not specific to neurodegenerative diseases. Other diseases such as muscular dystrophy are also associated with glutamine repeats, so that no specific utility can be based solely upon the presence of absence of such repeats.

Applicant's arguments against the Kashima's reference disclosure that a protein, not expressed in brain, but containing glutamine repeats, is irrelevant, misses the force and point being made in citation of Kashima. Kashima shows that no specific association of neurodegenerative disease and glutamine repeats is necessary. Kashima shows that entirely unrelated proteins may

have glutamine repeats but be have no specific association with neurodegenerative diseases. Given that no evidence of a specific association with any specific disease is provided in the specification for the claimed G713 protein, Kashima underlies a central point. Kashima found that glutamine repeats had no specific utility in the activity of MIL-2. Given the absence of any evidence, it is solely the object of further research to determine whether glutamine repeats play any role in the activity of G713, if that protein even has any activity whatsoever.

Applicant then argues the 112, first paragraph enablement rejection. Most of the arguments are identical to those already addressed. However, Applicant challenges the Wright papers showing of unpredictability in linkage of schizophrenia by citing Weinberger. The fact that there is significant debate over whether any particular chromosomal locations are actually linked to schizophrenia supports the unpredictability and does not undermine it. Weinberger does not identify any specific loci associated with schizophrenia but simply identifies a brain region associated with the disease, an entirely unrelated and irrelevant approach with regard to this application.

Therefore, given that the unpredictability of the linkage remains, the conclusion of undue experimentation will not be disturbed.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1637

May 21, 2002